recurrence risk assessment, especially when imaging results are unclear, and it can also provide reference for decision-making on adjuvant therapy (Pantel and Alix-Panabières, 2024).

This study will explore the current clinical application status of ctDNA-MRD in early solid tumors, analyze the common misunderstandings and actual challenges that may arise during its interpretation process, and also discuss the feasible paths for its combination with multimodal imaging. By integrating existing research evidence and related controversies, it is hoped to promote the transformation of ctDNA-MRD from a research tool to a standardized clinical application method, providing support for the precise treatment of early solid tumors.

2 Technical Foundation and ctDNA-MRD Detection Strategy

2.1 Biological source and dynamic characteristics of ctDNA

Circulating tumor DNA (ctDNA) accounts for a relatively small proportion in circulating free DNA (cfDNA). It mainly comes from the apoptosis, necrosis, or active release of tumor cells, carrying the unique characteristics of the tumor, such as somatic mutations, copy number alterations, and abnormal methylation. The fragments of ctDNA in plasma are mostly concentrated around 160-180 base pairs. This characteristic of the fragments is also utilized in fragmentomics and multi-omics MRD detection (Zhu et al., 2023). In the early stages of tumors or after patients undergo radical treatment, the proportion of ctDNA is usually less than 0.1%. It is indeed quite challenging to find such a very low-frequency signal in the background of a large amount of normal DNA (Semenkovich et al., 2023). Moreover, the half-life of ctDNA is only a few hours, which actually has an advantage as it can quickly reflect the treatment effect and the changes in post-treatment tumor burden.

Before tumor recurrence, the level of ctDNA tends to increase exponentially, and its doubling time is closely related to the detection sensitivity (Isbell et al., 2024). In various solid tumors, ctDNA-negative residual disease can usually indicate the risk of recurrence 4 to 12 months earlier than imaging examinations (Zhu et al., 2023). However, it should be noted that the release amount of ctDNA is affected by tumor type, growth location, blood supply, and treatment conditions. If the release amount is low or there is inflammation after surgery, it may lead to false-negative results in the detection (Chen and Zhou, 2023). Therefore, when interpreting the test results, one should not only consider a single test but also combine continuous monitoring and clinical reality for judgment (Semenkovich et al., 2023).

2.2 Main detection methods of ctDNA-MRD

The commonly used clinical strategies for ctDNA-MRD detection currently can be broadly classified into two categories: one is information-based detection based on tissues, and the other is non-tissue-based detection. Let's start with the information-based detection. In simple terms, it involves sequencing the primary tumor (usually accompanied by germline samples) to identify the patient-specific mutation sites, and then conducting ultra-deep tracking detection on plasma samples. By combining UMI tagging and error correction techniques, the false positive rate can be reduced even when the tumor burden is low (Kasi et al., 2022). This method has demonstrated clinical value in risk stratification and adjuvant treatment decision-making for diseases such as colorectal cancer (Chidharla et al., 2023), but it also has limitations-it relies on high-quality tissue samples, has high detection costs, and may miss newly emerging clonal variations (Semenkovich et al., 2023).

There is another type of non-organ-based detection. This method does not rely on specific organs and directly analyzes the free DNA in the plasma. Based on the preset mutation panel, copy number abnormalities, or methylation characteristics, it determines whether MRD exists. In recent years, by integrating fusion mutations and methylation signals, the ability of this method to detect ultra-low abundance ctDNA has been enhanced (Zhu et al., 2023; Quinn et al., 2025), and the operation is also simpler and more suitable for situations without tissue samples. However, it is prone to interference from background noise, especially the impact of clonal hematopoiesis. Therefore, it usually needs to be combined with white blood cell sequencing or filtered using strict algorithms (Semenkovich et al., 2023).

2.3 The impact of pre-analysis processing on detection accuracy

In the MRD detection scenario, the content of ctDNA is already extremely low. Therefore, the pre-analysis